REMARKS

Claims 1 and 5 are canceled herein, without prejudice or disclaimer, claims 2-6 are amended, and new claims 7-11 are added. Support for the amendments to claims 2-6 is found in the original claims. Support for new claims 7-11 is found in the specification, for example, on page 18, lines 21-23 and in the original claims. Hence no issues of new matter are presented. Upon entry of the Amendment, claims 2-4 and 6-11 will be all the claims pending in the application.

I. Response to Claim Rejections Under 35 U.S.C. § 112, 1st paragraph

Claims 1-5 are rejected under 35 U.S.C. § 112, 1st paragraph as allegedly being non-enabled for the entire scope of compounds having mGluR1 antagonistic activity. It is the Examiner's position that the specification is enabling for the particular compounds having mGluR1 antagonistic activity disclosed on page 7, line 21 to page 8, line 2 of the specification, but that it would require undue experimentation to determine what other compounds having mGluR1 antagonist activity would be suitable to practice the claimed invention. Specifically, the Examiner asserts that the examples and experimental results provided in the specification are insufficient to support the broad use of any mGluR1 antagonist, particularly in view of the unpredictability of the pharmaceutical art. In view of the factors set forth on pages 2-3 of the Office Action, i.e., the amount of direction or guidance provided, absence of working examples and the predictability of the art, the Examiner concludes that the specification fails to provide sufficient information to practice the claimed invention.

Applicants respectfully submit that claims 1 and 5 are canceled herein and claims 2-4 are dependent upon claim 6, which was indicated by the Examiner as being allowable if rewritten in independent form. Therefore, the rejection under 35 U.S.C. § 112, 1st paragraph, is moot.

Further, Applicants submit that the 35 U.S.C. § 112, 1st paragraph rejection does not apply to new claims 7-11. In this regard, Applicants respectfully submit that the Examiner has not considered all of the evidence related to each of the factors to be considered when making a determination of enablement as a whole. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The determination of whether undue experimentation would have been required is not a single factual determination, but is a conclusion that must be reached by weighing all of the factors to be considered. *Id.*

The Examiner lists all eight factors set forth in *In re Wands*, but bases her conclusion on a cursory review of evidence relating to only three of the factors, i.e., amount of guidance and direction, the number of working examples and the predictability of the art. Applicants submit that the amount of guidance or direction needed in the specification to enable the claimed invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427, F.2d 833,839 (CCPA 1970). The more that is known in the art about the nature of the invention, how to make and how to use the invention, the less information that needs to be explicitly set forth in the specification. Further, if one of ordinary skill in the art can extrapolate the disclosed or known results to the claimed invention, then there is predictability in the art. Thus, Applicants respectfully submit that the claimed invention is sufficiently enabled by the present specification in view of the following.

(1) Quantity of experimentation necessary

For the purpose of the present invention, the compounds known as mGluRl antagonists in the art, e.g., patents, non-patent literature, etc., can be systemically administered to generally used nerve-ligated model animals or STZ-induced diabetic neuropathic pain model animals described in the specification. Thus, undue experiments are not required.

(2) Amount of direction or guidance provided

The present specification cites literature disclosing the compounds that had been known as mGluRl antagonists at the time of the filing date of this application. In addition, with respect to the experimental methods, Test Examples 1 and 2 respectively disclose two types of test methods for neuropathic pain models that correspond to the claims. Accordingly, the amount of direction and guidance are sufficient for one of ordinary skill in the art.

(3) Presence or absence of working examples

It has been established that the specification need not contain an example of the invention if the invention is otherwise disclosed so that one of ordinary skill in the art will be able to practice it without undue experimentation. *See* MPEP 2164.02, citing *In re Borkowski,* 42 F.2d 904, 908 (CCPA 1970). In this case, examples of two compounds are shown in the specification. It is also described in the specification that other compounds can be subjected to experiments in the same way and therefore undue experimentation is not required as discussed above. Accordingly, the working examples in the present specification are sufficient to enable one of ordinary skill in the art to practice the claimed invention.

(4) Nature of the invention

The present invention relates to a new method for treating neuropathic pain by systemic administration, using a compound having antagonistic activity against the mGluR1 receptor.

(5) State of the prior art and (7) Predictability of the art

At the time of the filing date of the present application, the state of the art was that the intraspinal administration of an mGluRl antagonist to nerve-ligated models showed a prophylactic effect but did not provide a therapeutic effect in the maintenance of neuropathic pain once generated (Fisher et al. Pain 77, 59-66, 1998; cited on PTO 1449 filed on January 18, 2002).

On the other hand, it was not known that therapeutic effects could be obtained by systemic administration.

(6) Relative skill of those in the art

Systemic administration is a general method for administration. Accordingly, systemic administration according to the present invention can be sufficiently carried out by one skilled in the art who reads the disclosure of the present application.

(8) Breadth of the claims

The scope of the claims is not unduly broad. There are many U.S. patents which have been granted for an antagonist for a specific receptor by showing only one Example (e.g., US 6,433,018, US 6,441,027, US 6,448,280, US 8,451,780, US 6,462,065, US 6,462,066, etc.).

Further, Applicants submit the attached Declaration under Rule 132, which provides additional examples of compounds within the scope of the present invention that are not shown in Examples in the specification, but which have the same effect. The data provided in the Declaration shows a correlation between *in vitro* binding affinity and the *in vivo* effective dose of various compounds having mGluR1 antagonistic activity. Therefore, undue experimentation would not be required by one of ordinary skill in the art.

Accordingly, Applicants respectfully request withdrawal of the rejection.

II. Response to Claim Rejections Under 35 U.S.C. § 112, 2nd paragraph

Claims 1-5 are rejected under 35 U.S.C. § 112, 2nd paragraph as allegedly being indefinite based upon the recitation of "a compound having mGluR1 antagonistic activity". The Examiner asserts that the recitation fails to clearly set forth the metes and bounds of the claimed invention.

Applicants respectfully submit that claims 1 and 5 are canceled and claims 2-4 are amended to depend from amended claim 6, which was indicated as allowable if rewritten in independent form. Therefore the rejection is considered moot. Further, Applicants note that the breadth of a claim does not necessarily render the claim language indefinite.

As applied to new claims 7-11, Applicants respectfully submit that new claim 7 recites "a compound having mGluR1 antagonistic activity and having no activity on Group II and Group III of metabotropic glutamate", which is readily understood by one of ordinary skill in the art when read in light of the specification, and therefore is not indefinite.. Accordingly, Applicants respectfully request withdrawal of the rejection.

III. Response to Claim Rejections Under 35 U.S.C. § 102

Claims 1-3 are rejected under 35 U.S.C. § 102(b) as being anticipated by Fisher et al, or Neugebaur et al or Salt et al. Each of Fisher et al, Neugebaur et al and Salt et al are relied upon for the disclosure compounds having mGluR1 antagonistic activity in effective amounts which are said to be useful in pharmaceutical compositions and for treating neuropathic pain.

Claim 1 is canceled and claims 2-3 are amended to depend from amended claim 6, which was indicated as allowable if rewritten in independent form. Therefore the rejection is moot.

Further, the rejection does not apply to new claims 7-11 since none of the references cited teaches the presently claimed invention. Specifically, none of the cited references teaches a composition comprising compounds having mGluR1 antagonistic activity which is administered systemically and which has a therapeutic effect on neuropathic pain or a method of improving neuropathic pain which comprises systemically administering a compound having mGluR1 antagonistic activity as claimed.

1. Fisher et al

As explained in the specification of the present application, Fisher et al discloses that Group I mGluRl antagonists participate in the development of the pain threshold but do not participate in the maintenance of the pain threshold which has already been generated. This description in Fisher et al suggests that Group I mGluRl antagonists have prophylactic effects and do not have therapeutic effects. On the other hand, therapy of neuropathic pain according to the present invention is a relieving effect from the neuropathic pain which already exits. This

therapeutic effect of the present invention corresponds to the description in Fisher et al that is suggested to be non-effective. Further, the reference discloses intraspinal administration, which is a topical method of administration, and does not disclose a systemic administration. Moreover, neuropathic pain induced by diabetes is not taught by Fisher et al. Therefore, Fisher et al does not teach all elements of the present claims, and therefore does not anticipate the claimed invention.

2. Neugebauer et al

Neugebauer et al disclose that AIDA, which is a selective mGluR1 antagonist, inhibits noxious stimuli transmission by pinch and press and capsaicin-induced central sensitization. In this reference, normal rats having no neuropathy were used and AIDA activities were measured under anesthesia, but these experimental conditions do not reflect neuropathic pain pathology. In addition, while capsaicin accelerates sensory nerve activities by acute application but inhibits the same by chronic application (Holzer P., Capsaicin; Cellular targets, Mechanisms of Action, and Selectivity for Thin Sensory Neurons, Pharmacol. Rev. 43 (1991) 143-201; copy attached), both of them do not reflect "neuropathy" which is a pathology of the neuropathic pain. Accordingly, Neugebauer et al does not teach all of the elements of the claims, and therefore does not anticipate the claimed invention.

3. Salt et al

Salt et al discloses that the disclosed mGluRl antagonists relate to inhibition of nociceptive reaction. In this reference, normal rats having no neuropathy were used, and effects of (S)-4CPG on the air ject (innocuous stimulus) and heat stimuli (noxious stimulus) were

evaluated under anesthesia. The experimental conditions do not reflect neuropathic pain pathology. In addition, (S)-4CPG is not a selective mGluRl antagonist. Accordingly, Salt et al does not teach all of the elements of the claims, and therefore does not anticipate the claimed invention.

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 102.

IV. Response to Rejections Under 35 U.S.C. § 103

Claim 4-5 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Fisher et al, Neugebaur et al and Salt et al.

The Examiner recognizes that none of the cited references expressly disclose oral or systemic administration of a pharmaceutical composition having mGluR1 antagonistic activity. It is the Examiner's position that one of ordinary skill in the art would have been motivated to orally or systemically administer a pharmaceutical composition comprising compounds having mGluR1 antagonistic activity as disclosed in the prior art because the compounds were known to be administered broadly at the time of the present invention. The Examiner further states that the determination of routes of administration is considered well within the skill of the artisan.

The Examiner also states that it would have been obvious to one of ordinary skill in the art to select premenstrual syndrome from the group of disorders to be treated using these compounds (see page 6, 6th paragraph) which is not considered to be relevant to any of the references or to the claimed invention. If Applicants' understanding is incorrect, Applicants

respectfully request further explanation from the Examiner as to how this statement is relevant to the present claims.

Claim 5 is canceled herein and claim 4 is amended to depend from amended claim 6, which was indicated as allowable if rewritten in independent form. Thus the rejection is considered moot.

As applied to new claims 7-11, Applicants respectfully traverse the rejection and submit that the Examiner has not made a *prima facie* showing of obviousness. As stated above with respect to the rejections under 35 U.S.C. § 102, the cited references do not teach or suggest all elements of the claims.

Fisher et al discloses a prophylactic effect of the disclosed mGluR1 antagonists, but teaches away from the claimed therapeutic effect. Neugebauer et al and Salt et al merely disclose that mGluR1 antagonists have an effect on inhibiting noxious stimulus transmission in normal rats having no neuropathy.

In addition, none of the cited references teaches or suggests a systemic route of administration. Since about 1998, the relationship between neuropathic pain and mGluR1 Group I antagonists has been reported. In 1992 and 1994, it was reported that mGluRl receptors are highly expressed in the thalamus and exist in relay neurons that transmit noxious information to the cerebral cortex. (Neuron 9, 259-270, 1992 (copy attached); Neurochem. Int., 24, 451-458, 1994(cited opn PTO 1449 filed on January 18, 2002)). Although this information was available, the experiments for neuropathic pain had been carried out by intraspinal administration. This fact shows that the intraspinal administration was the state of art in the area of neuropathic pain

and mGluR Group I. Thus, it proves that the choice of systemic administration as a route for administration was quite unobvious to one skilled in the art. Thus, all elements of the claimed invention are not taught or suggested by the cited references. Therefore, one of ordinary skill in the art would not have had a reasonable expectation of success in achieving the claimed invention based upon the disclosure of the cited references, taken alone or in combination.

Accordingly, Applicants respectfully request withdrawal of the rejection.

V. Claim Objection

Claim 6 is objected to as dependent upon a rejected base claim but would be allowable if rewritten in independent form.

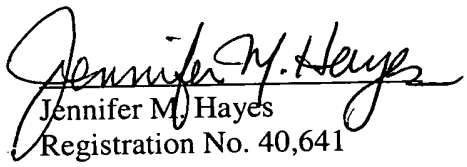
Applicants thank the Examiner for the indication of allowable subject matter and submit that claim 6 is rewritten in independent form. Claims 2-4 are dependent thereon and are allowable for at least the same reasons. Accordingly, Applicants respectfully request withdrawal of the objection.

VI. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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Date: December 30, 2002

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 1 and 5 are canceled.

The following claims are amended.

2. (Amended) The pharmaceutical composition according to claim ~~1~~6, wherein the neuropathic pain is ~~a neuropathic pain~~ induced by diabetes or compression of nerves.

3. (Amended) The pharmaceutical composition according to claim ~~1~~2, wherein the neuropathic pain is ~~a neuropathic pain~~ induced by diabetes.

4. (Amended) The pharmaceutical composition according to claim ~~1~~6, wherein the systemic administration method is oral administration.

6. (Amended) ~~The~~ A pharmaceutical composition for use in treating neuropathic pain, which is administered by a systemic method of administration and which comprises a compound having mGluR1 antagonistic activity~~according to claim 1~~, wherein the compound having mGluR1 antagonism is a compound selected from 6-amino-N-cyclohexyl-N,3-dimethylthiazolo[3,2-a]benzoimidazole-2-carboxamide dihydrochloride and (+)-(1*R*,2*S*)-6-amino-N-methyl-N-(2-methylcyclohexyl)thiazolo[3,2-a]benzoimidazole-2-carboxamide dihydrochloride.

Claims 7-11 are added as new claims.